

DETAILED ACTION

1. This application is a 371 of PCT/JP04/09001 filed 06/25/2004 and claims priority to JAPAN 2003-184359 filed 06/27/2003.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 365(c) as follows:

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 6/27/2003. It is noted, however, that applicant has not filed a certified copy of the 2003 application as required by 35 U.S.C. 119(b).

Claim Rejections/Objections Withdrawn

3. The rejection of claims 3, 4, 10, 11 under 102(b) over by Ucciani et. al. is withdrawn since it was pointed out that rhodium is not a limitation of these particular claims.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

3. The rejection of claims 1-2, 9, under 35 U.S.C. 102(b) as being anticipated by Ucciani et. al. is maintained. Applicant's representative has argued that Ucciani does not disclose using carbon monoxide in the subsequent conversion of 2-nitroaldehyde" to skatole (the 3-methyl indole). This is factually incorrect. Some relevant portions of Ucciani are reproduced from the original image below (with underlining added for emphasis).

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complexes and precursors. Whatever the conditions, even under high pressure and at high temperatures, the complexes $\text{RhCl(PPh}_3)_3$ and $\text{RhCl(CO)(PPh}_3)_2$ lead to a low conversion of 2-nitrostyrene. Clusters such $\text{Rh}_4(\text{CO})_{12}$ and $\text{Rh}_6(\text{CO})_{16}$ are quite ineffective. In previous work we had found that the most active catalysts were produced *in situ* from supported rhodium precursors such as $\text{Rh/Al}_2\text{O}_3$ and Rh/C . With Rh/C , at 80°C and under a pressure of 160 atm [$p(\text{CO}) = p(\text{H}_2)$] in benzene, (1) is completely converted within 1–2 h into the 2-nitroaldehyde (2) (*ca.* 60%), other expected products (3) (5%) and (4) (5%), and a by-product (*ca.* 28%) (g.l.c. analysis), which was identified as 2-aminoacetophenone on the basis of m.s. and n.m.r. data.

These results suggested that supported rhodium should be a convenient catalytic precursor for skatole synthesis, in that it is both selective for formation of the branched-chain aldehyde and able to promote nitro-group reduction. Higher temperatures did lead to the conversion of (2) and (3) into (4).

“Higher temperatures did lead to the conversion of (2) and (3) into (4).” Clearly Ucciani converted the compound 2 which is a precise compound of formula (I) of the instant claims to the compound 4, which is an exact same compound of formula (2). Ucciani used CO, H_2 , and rhodium catalysts, rhodium catalysts that are the same as those of the instant claims.

Another argument is that the new limitation “complex” somehow distinguishes the claimed catalyst from the catalysts of Ucciani. There is no complete definition of “complex” in

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the specification, although some examples are given. The examiner submits the following definitions of complex, although complex has no one accepted meaning in chemistry.

According to IUPAC a "complex" is:

"A molecular entity formed by loose association involving two or more component molecular entities (ionic or uncharged), or the corresponding chemical species. The bonding between the components is normally weaker than in a covalent bond. The term has also been used with a variety of shades of meaning in different contexts: it is therefore best avoided when a more explicit alternative is applicable. In inorganic chemistry the term 'coordination entity' is recommended instead of 'complex'." "Complex" IUPAC Goldbook online: "<http://goldbook.iupac.org/C01203.html>" accessed 10/27/2009.

According to wikipedia a "complex" is:

"Metal complexes, also known as coordination compounds, include all metal compounds, aside from metal vapors, plasmas, and alloys. The study of "coordination chemistry" is the study of "inorganic chemistry" of all alkali and alkaline earth metals, transition metals, lanthanides, actinides, and metalloids. Thus, coordination chemistry is the chemistry of the majority of the periodic table. Metals and metal ions only exist, in the condensed phases at least, surrounded by ligands." Online "Coordination complex" wikipedia "http://en.wikipedia.org/wiki/Coordination_complex", accessed 10/28/2009

All the metal compounds of Ucciani meet these definitions. Supported rhodium catalysts are in fact complexes. Regardless rhodium carbonyl complexes are involved in these reactions as evidenced by the quotation cited in the 102 rejection. There appears to be some disparagement of the yields with some the catalysts of Ucciani, however such a disparagement is not relevant since the instant claims cover exactly the same catalysts. The argument that "the prior art clusters such as $\text{Rh}_4(\text{CO})\text{I}_2$ and $\text{Rh}_6(\text{CO})\text{Cl}_6$ are quite ineffective", seems to be an admission that at least some of the instant claims fail to meet the requirements of 112 1st paragraph, these statements may form the basis of an enablement rejection.

The rejection of claims 1-3, 7, 8, 9, 10, 13-14, 17, 18 under 35 U.S.C. 102(b) as being anticipated by U.S. 3,682,901 is maintained. The only argument put forth in this rejection is that

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the '901 catalysts are not complexes. The examiner disagrees based on the failure of "complex" to distinguish the art of record from the instant claims. All the metal compounds of the '901 patent meet this limitation, as per the art recognized definitions of "complex" (*vide supra*).

The rejection of claims 1-20 under 35 U.S.C. 103(a) as being obvious over Ucciani et. al. OR U.S. 3,682,901 AND Sundberg, R.J. AND Cennini et. al. AND Tafesh et. al., is maintained. A good portion of this rejection is based on the misinterpretation of "complex" as shown above. As these references are in fact anticipatory, anticipation is the epitome of obviousness.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). There appears to be some disparagement of the yields with some the catalysts of the Cennini reference, however such a disparagement is not relevant since the instant claims cover exactly the same catalysts. An argument of unexpected results, must be commensurate with the scope of the claims. Currently the claims embrace all known Group VIII metal complexes, which is not consistent with the disclosure of a few catalysts. With regard to the unexpected results, according to Tafesh the use of these metal complexes in catalytic carbonylative nitro reduction is recognized as industrially important, versatile, and has a "low cost". Tafesh also explains that one would choose these reagents over reductants like the metal hydrides, catalytic hydrogenation (or Fe/AcOH as in JP47-38963), in order to avoid potential side reactions. Reduction in side products would naturally lead to increases in yield, thus the fact that the instantly claimed process gives an increased yield is actually expected. Expected beneficial results are evidence of obviousness of a

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claimed invention, just as unexpected results are evidence of unobviousness thereof.” In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967) (resultant decrease of dental enamel solubility accomplished by adding an acidic buffering agent to a fluoride containing dentifrice was expected based on the teaching of the prior art); *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989).

Claim Rejections - 35 USC § 102

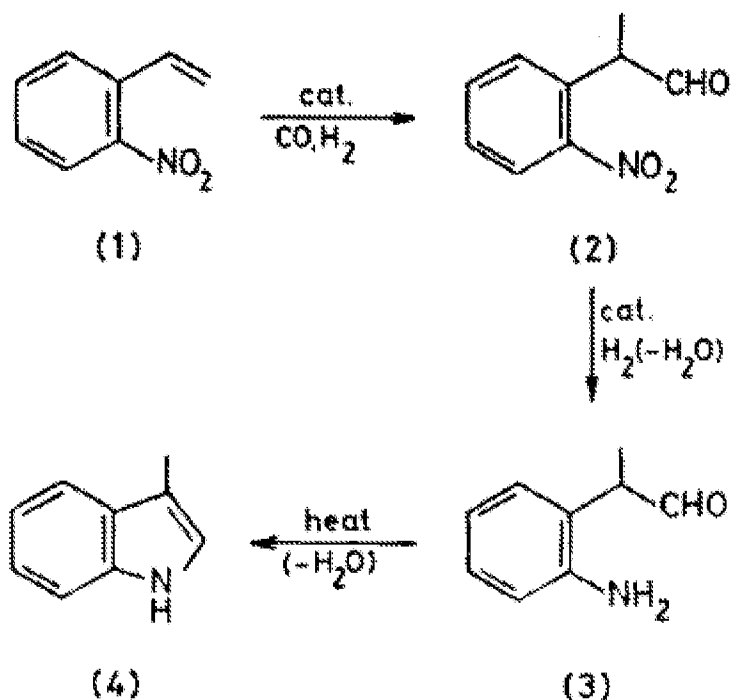
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-2, 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Ucciani et. al. “Catalytic Synthesis of 3-Substituted Indoles using CO as Building Block and Supported Rhodium as Catalyst.” *Journal of the Chemical Society Chemical Communications*, **1981**, 82-83. Ucciani practiced the process of the instant claims where R² is a methyl group, n is 0, and R¹ is H (i.e. the conversion of 2 to 4, skatole).

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“The expected reaction pathway to skatole can be summarized as in the Scheme, and we wished to discover a method that would lead to highly selective formation of the branched-chain aldehyde (2), and a catalyst which would be able to perform the hydroformylation and nitro-group reduction in one step.”

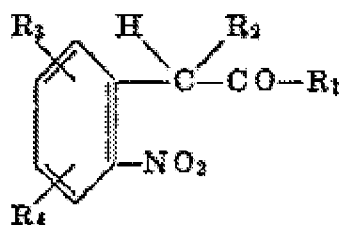
“Our results indicate the following conclusions. (i) Under severe hydroformylation conditions supported rhodium can act as a reservoir of rhodium carbonyl complexes and as a mass contact able to activate molecular hydrogen, and (ii) a catalytic route to 3-substituted indoles from 2-nitrostyrenes and carbon monoxide is available,”

Of course the conditions of Ucciani et. al. are hydroformylation conditions i.e. (H_2 and CO), however since CO is present in the reaction the instant claims are anticipated.

4. Claims 1-3, 7, 8, 9, 10, 13-14, 17, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. 3,682,901. U.S. '901 describes the process of the instant claims at column 1:

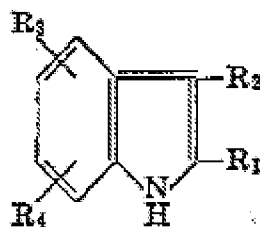
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Process for preparing 2-substituted indoles (I) by reacting carbon monoxide at elevated temperature and super-atmospheric pressure in the presence of a co-catalyst composition, of which 5% palladium on carbon with a Lewis acid such as ferric chloride is representative, with an o-nitrobenzyl ketone (II):



II

to form:



I

where R_1 is alkyl, aralkyl, aryl or styryl; R_2 is hydrogen, alkyl or aryl, and R_3 and R_4 typically are hydrogen or alkyl.

Several catalysts are mentioned as part of the invention:

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The catalyst for the reaction of this invention comprises a noble metal and a Lewis acid as defined in the reference book by Jack Hine, "Physical Organic Chemistry," 1962, McGraw-Hill Book Company, New York. The noble metal may be used either in a metallic or a chemically combined state. It may be employed either with or without a physical support. Among the noble metals which may be employed are platinum, palladium, rhodium, osmium, silver, gold, iridium, and mercury. Palladium is preferred. Among the chemical forms of these metals which can be used are the oxides, sulfates, nitrates and halides, as for example: platinum oxide, rhodium oxide, platinum chloride, rhodium chloride, platinum nitrate, platinum sulfate and the corresponding palladium compounds. The noble metals or compounds thereof may be employed singly or in admixture.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ucciani et. al. "Catalytic Synthesis of 3-Substituted Indoles using CO as Building Block and Supported Rhodium as Catalyst." *Journal of the Chemical Society Chemical Communications*, **1981**, 82-83 OR U.S. 3,682,901 AND Sundberg, R.J. *The Chemistry of Indoles*, Academic: 1970, pg 176 AND Cennini et. al. Chapter 5 of CATALYTIC REDUCTIVE CARBONYLATION OF ORGANIC NITRO COMPOUNDS Kluwer: 1997, pgs 177-246 AND Tafesh et. al. "A Review

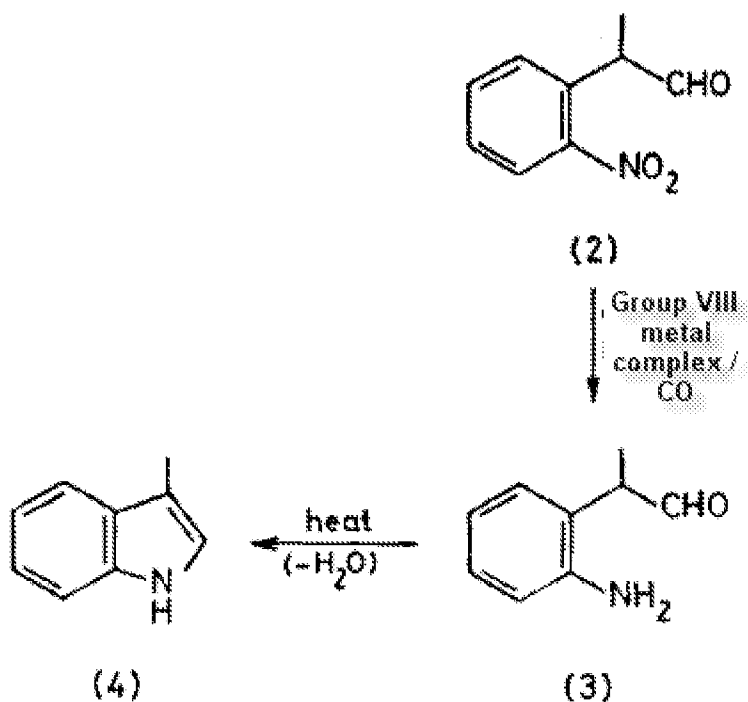
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of the Selective Catalytic Reduction of Aromatic Nitro Compounds into Aromatic Amines, Isocyanates, Carbamates, and Ureas Using CO" *Chemical Reviews* **1996**, 96, 2035-2052.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

- A) Determining the scope and contents of the prior art.
- B) Ascertaining the differences between the prior art and the claims at issue.
- C) Resolving the level of ordinary skill in the pertinent art.
- D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims are drawn towards a method of making indoles, in the narrowest embodiment (i.e. where R1 is Me, R2 is H) this is a method making 1-methyl indole, n is 0. As shown below, where R2 is Me, R1 is H:



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Sundberg shows that this is a very old reaction, from page 170 “The chemical or catalytic reduction of an *o*-nitrobenzyl ketone generates an *o*-aminobenzyl ketone which can subsequently cyclize and aromatize by dehydration to an indole.” Ucciani et. al. accomplished this reaction with rhodium carbonyl complexes (see the 102 (b) rejection supra). The only claims that are not anticipated (claims 3-8, 10-20) either recite a catalyst other than ruthenium based (claims 5, 12, 16, 20), or amount to a position isomer of the starting material and product of Ucciani (claims 6-8, 13-15, 17-19, where R¹ and R² have switched positions). The '901 document teaches essentially the same reaction (see the 102 (b) rejection supra), but with Group VIII metals with various lewis acid co-catalysts. Both Cennini and Tafesh teach that a diverse array of group VIII transition metal carbonyl complexes (including Pt and Pd with phosphine ligands) may be used in transformations of this type. Neither the Ucciani et. al. paper nor the '901 patent mention the catalysts of Tafesh or Cennini because they were not yet known to catalyze this transformation at the time. The presence of the methyl group in either the 1 or 2 position (i.e. starting from the methyl ketone or the aldehyde) will have little consequence on the outcome of the condensation reaction.

According to Tafesh this type of nitro reduction is recognized as industrially important, See conclusions, “The use of CO in the reductive carbonylation of aromatic nitro compounds is very important not only from an academic point of view but also from an industrial one. Its versatility, low cost, and ease of accessibility make it very attractive to the researcher. Its application should find use in the production of agricultural chemicals, pesticides, high performance plastics, polyurethanes, elastomers, and adhesives, and its selective formation of functionalized products can find use in pharmaceuticals as well as the fine chemical industry. It

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was found that for each reaction and even for each substrate the catalyst system has to be optimized in view of metal complex, ligand, counterion, and cocatalyst.”

Tafesh also explains that one would choose these reagents over reductants like the metal hydrides, catalytic hydrogenation (or Fe/AcOH as in JP47-38963), in order to avoid potential side reactions, see pg. 2043 “Aromatic amines are important intermediates in the fine chemical, dye, and pigment industry.⁸⁷ Aromatic amines are produced by reduction of the corresponding nitro aromatics with a metallo hydride reagent or by catalytic hydrogenation.⁸⁸ The selective reduction of nitro aromatic groups in the presence of sensitive functional groups, e.g. carbonyl, cyano, chloro, and alkenic groups, with hydrogen is often difficult, because these sensitive functionalities are reduced faster with hydrogen than the nitro group.⁸⁹”

The instant claims recite only an obvious variant of an old process. The replacement of catalytic hydrogenation or the noble metal/lewis acid mixture with group 8 transition metal carbonyl complexes with carbon monoxide reductants in the transformation of the nitro group was well established and favored. It would be obvious to improve upon the processes of the Ucciani et. al. paper or the '901 patent to improve yields (by decreasing side products), and save money.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Monday-Friday 9:00 A.M. to 6:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/

Primary Examiner, Art Unit 1625